Case Report

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Harlequin Ichthyosis: Prenatal Diagnosis of a Rare Yet Severe Genetic Dermatosis

Obstetrics and Gynaecology Section

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ABSTRACT

Harlequin Ichthyosis (HI) is an extremely rare genetic skin disorder. It is the most severe type of ichthyosis. It is characterized by thickened, dry, rough and armor like plates of skin with deep cracks in between. Alternative names for HI include- keratosis diffusafetalis, ichthyosis congenital, icthyosis fetalis, harlequin fetus and icthyosis congenital gravior. It is an autosomal recessive disorder with the majority of affected individuals being homozygous for mutation in the ABCA 12 gene. This condition presents with a wide range of severity and symptoms. Affected neonates usually do not survive beyond first few days of life. We are presenting prenatal diagnosis of a case of this rare condition.

Keywords: Eclabium, Ectropion, Harlequin fetus

CASE REPORT

A 31-year-old multiparous lady, gravida 3, para 2, live 1, 1 early neonatal death with second degree consanguineous marriage, presented to us at eight weeks for routine antenatal checkup.

In her first pregnancy, she had delivered a preterm, male baby at 36 weeks gestation, which died after 4 days of life. At birth, baby was found to have dry, scaly skin all over the body, wide open mouth with protruding lip, hypoplastic ears and nose and contractures of fingers and toes. A clinical diagnosis of harlequin ichthyosis was made. The couple underwent genetic counseling, where they were explained about the genetic etiology of the problem and the risk of recurrence in subsequent pregnancies. Option of fetal DNA banking for prenatal diagnosis in next pregnancy was offered to the parents but was not done due to financial constraints in the family.

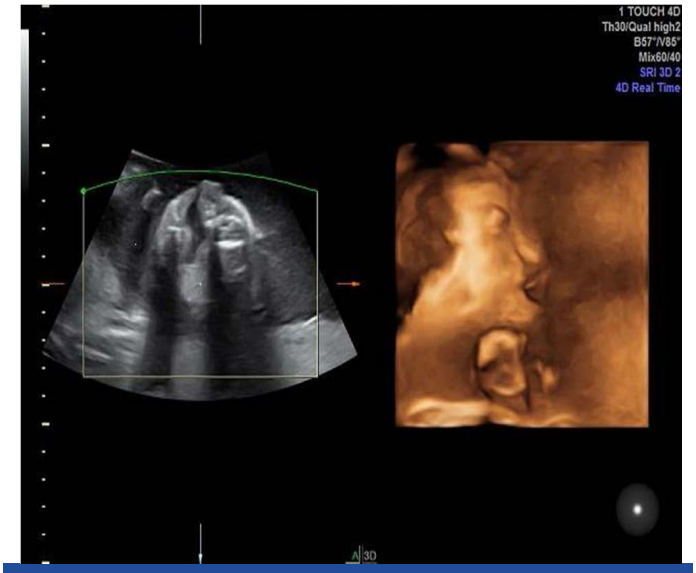
Her second pregnancy was unremarkable and she delivered a healthy male baby at term with no stigmata of HI.

In her present pregnancy, morphology scan done at 20 weeks gestation was unremarkable. In view of her prior history, an ultrasound with three dimensional and four dimensional real time sonography was performed at 26 weeks, which showed abnormal facial features with eversion of the eyelids (ectropion), eversion of lips (eclabium), short foot length, incurved toes, clenched fist, poor delineation of nostrils and polyhydramnios [Table/Fig-1-3]. Fetal biometry corresponded to 27 weeks gestation.

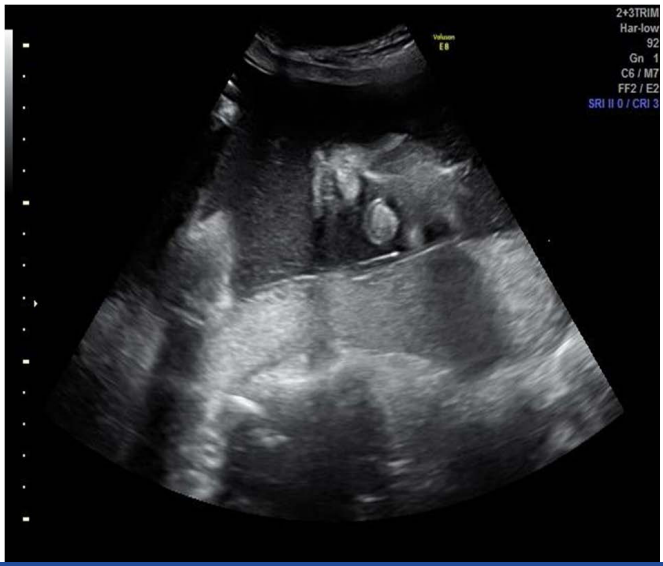
With probable diagnosis of HI, she was referred to perinatal medicine clinic where she received counseling from a multi-disciplinary team comprising of a geneticist, perinatologist and neonatologist. They were explained about poor prognosis of the baby in view of early manifestation of the disease and chances of severe pulmonary hypoplasia. The family opted to terminate the pregnancy and she was induced with prostaglandin and delivered a fresh stillborn baby with features suggestive of HI [Table/Fig-4,5]. Fetal blood was collected for DNA banking and planned for mutation analysis of ABCA 12 gene. Skin biopsy was sent for histopathological examination [Table/Fig-6,7].

DISCUSSION

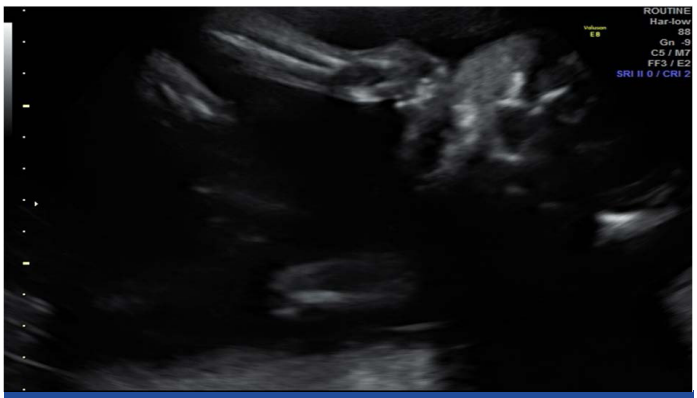
Harlequin ichthyosis is a rare, severe form of skin disorder associated with massive thickening of skin over entire body [1]. The first case was reported in 1750 by Reverend Oliver Hart. The overall incidence is 1 in 300,000 births [2,3].



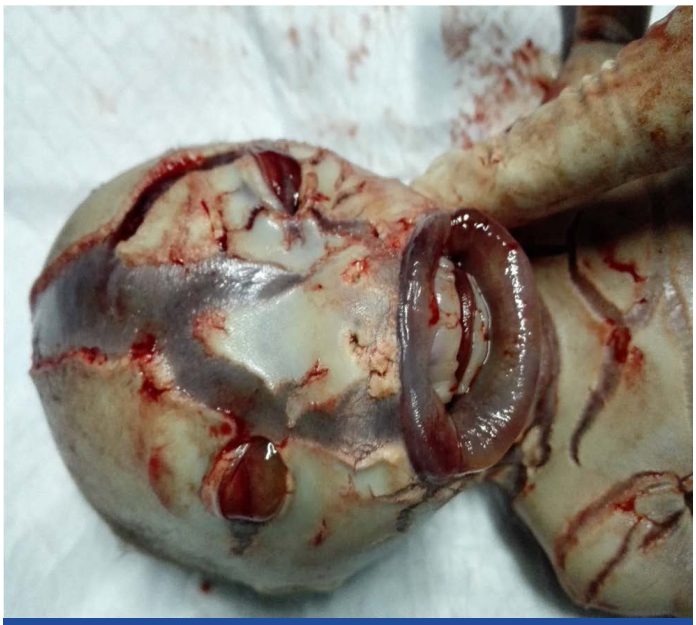
[Table/Fig-1]: A 3 Dimensional image showing abnormal protrusion on eye (ectropion), fixed open mouth and nasal hypoplasia



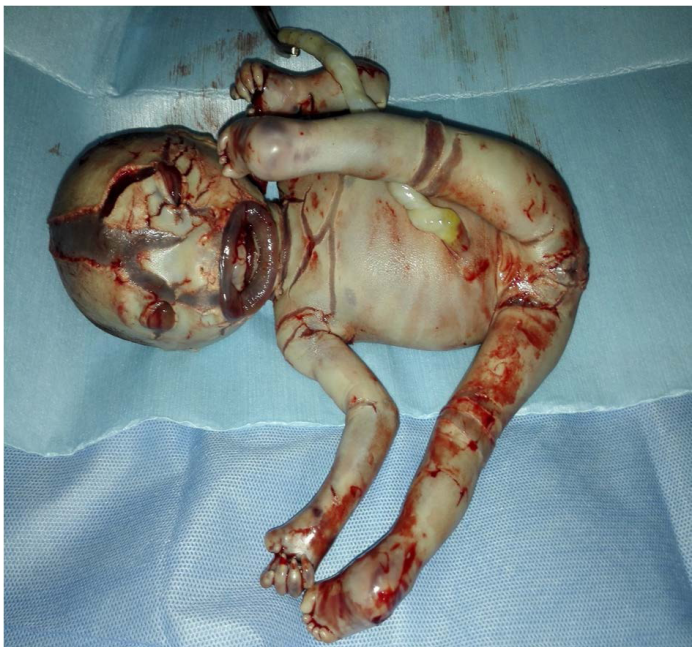
[Table/Fig-2]: B mode sonogram displays a flat profile and conjunctival protrusion (ectropion)



[Table/Fig-3]: Ultrasonographic picture showing clenched fist and hydroamnios

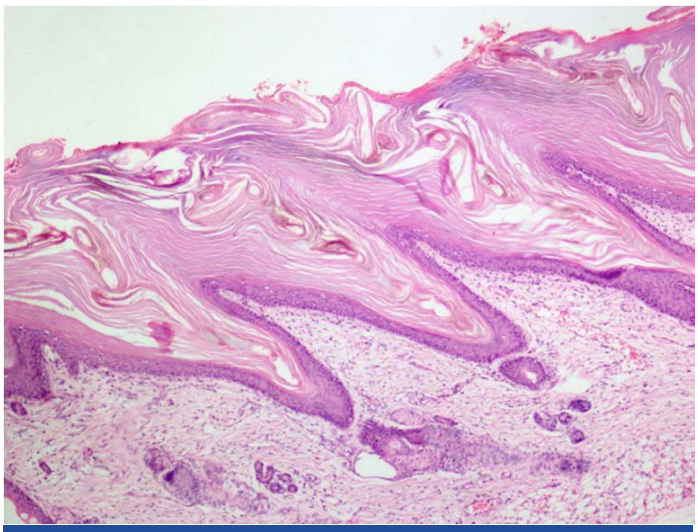


[Table/Fig-4]: Showing Harlequin fetus with characterstic clown like facies, with ectropion, eclabium and under developed nose. Note the coat of armour like appearance with shiny plates and fissures

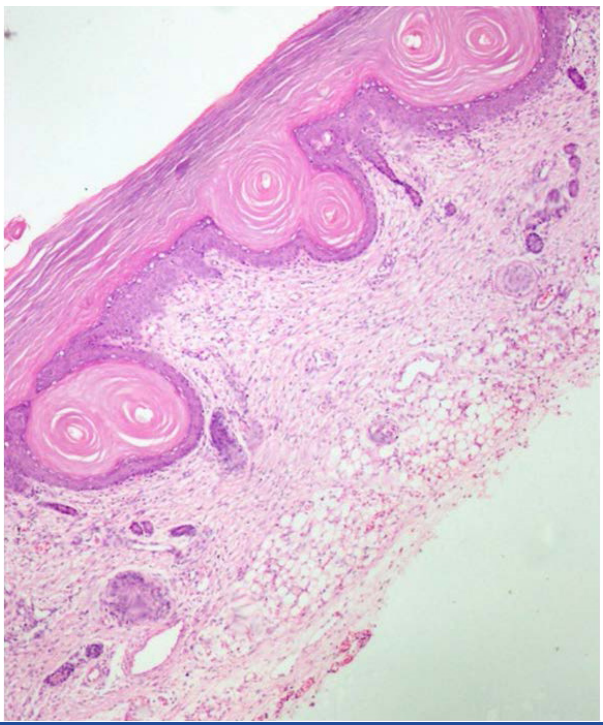


[Table/Fig-5]: Showing incurved toes, short foot length and clenched fist typical of Harlequin fetus

The inheritance is autosomal recessive with 25% chance of recurrence in subsequent pregnancies. HI is due to disease causing variants in Adenosine Triphosphate Binding Cassette Transporter Protein A12 (ABCA12) gene on chromosome 2 [1,3-6]. This gene



[Table/Fig-6]: Patho slide: Extensive hyperkeratosis in stratum corneum layer of the patiet's epidermis



[Table/Fig-7]: Electron microscopy; atypical intra epidermal vesicles /premature keratinistion

carries information for transportation of lipids to keratinocytes of cutaneous layer. In this congenital epidermal disorder there is abnormal and diffuse hyperkeratosis and loss of protective skin barrier. This in turn results in inadequate removal of scales from skin and leads to deposition of dead skin making it hyperkeratotic and more prone to infections due to loss of its protective barrier function [3,7]. Currently more than 70 disease causing variants have been described in the literature and new novels variants are being described every year around the world [3].

The clinicopathological features of this skin disorder are very typical. There is characterstic appearance of profound thick, shiny, white hyperkeratotic plates with deep erythematous diamond shaped cracks [3]. A clown like facies is the result of thick and tight pulled up skin causing ectropion, eclabium, hypoplastic flat nose and rudimentary ear appendages [Table/Fig-4]. Massive skin thickening results in flexion contractures in upper and lower limbs leading to restricted mobility and a “coat of armour” appearance [Table/Fig-5] [7]. Clenched fists and and incurved toes are also present [Table/Fig-6]. Late phenotypic expression of this condition may lead to missed/delayed diagnosis on prenatal scans [3,6].

This condition is associated with preterm birth. Affected neonates usually not survive beyond first few days of life.

If undiagnosed prenatally, there are several neonatal complications associated with this condition at birth. Breathing difficulty and respiratory infections are secondary to restricted chest expansion and prematurity [3,7]. Thickened, cracked skin leads to impaired temperature regulation and increased risk of infections. Wide mouth causes feeding difficulty. Affected infants have problems in maintaining electrolyte balance and dehydration is the most frequent complication. Intravenous access is difficult, umbilical cord cannulation is usually recommended for fluid monitoring and drug administration.

Therefore multidisciplinary team management is recommended. There is no specific cure from this disorder, but complications can be prevented and tackled with advance medical care which, unfortunately, is not available in the developing world.

Diagnosis can be confirmed by testing for mutation in ABCA12 gene in the affected fetus. DNA based analysis for prenatal testing is reliable and conclusive [8]. Prenatal diagnosis with Chorionic Villus Sampling (CVS) and amniotic fluid cells analysis is advised in women with previous affected baby. Skin biopsy is not currently recommended for prenatal diagnosis [3,7]. Antenatal USG, especially 3D USG [9] is another modality of prenatal diagnosis but late phenotypic expression of the disease poses a challenge for timely detection and further management.

CONCLUSION

HI is a rare skin disorder. It follows autosomal recessive mode of inheritance. Prenatal diagnosis should be offered to women with previously affected babies. DNA analysis for ABCA12 mutation will clinch the diagnosis. Characteristic features on prenatal USG tend to appear late so the scans should be repeated even when the second trimester anatomy scan is normal and can help in a situation when a DNA diagnosis is unavailable.

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